A phenotypic small-molecule screen identifies an orphan ligand-receptor pair that regulates neural stem cell differentiation.

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Public Summary:
High-throughput identification of small molecules that selectively modulate molecular, cellular, or systems-level properties of the mammalian brain is a significant challenge. Here we report the chemical genetic identification of the orphan ligand phosphoserine (P-Ser) as an enhancer of neurogenesis. P-Ser inhibits neural stem cell/progenitor proliferation and self-renewal, enhances neurogenic fate commitment, and improves neuronal survival. We further demonstrate that the effects of P-Ser are mediated by the group III metabotropic glutamate receptor 4 (mGluR4). siRNA-mediated knockdown of mGluR4 abolished the effects of P-Ser and increased neurosphere proliferation, at least in part through upregulation of mTOR pathway activity. We also found that P-Ser increases neurogenesis in human embryonic stem cell-derived neural progenitors. This work highlights the tremendous potential of developing effective small-molecule drugs for use in regenerative medicine or transplantation therapy.

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